News and Views from the Literature

Prostate Cancer

The Predictive Capability of Prostate-Specific Antigen Kinetics

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In the last decade, it has been recognized and repeatedly demonstrated that prostate-specific–antigen (PSA) kinetics are an important indicator of the aggressiveness of prostate cancer. Specifically, PSA pretreatment velocity and PSA doubling time (PSADT) after PSA failure are major factors in determining the prognosis of men with prostate cancer. Rapid PSA velocity ($>$ 2.0 ng/mL/y) and short PSADT ($<$ 10–12 months) are associated with poor prognosis.

Risk of Prostate Cancer-Specific Mortality Following Biochemical Recurrence After Radical Prostatectomy

Freedland SJ, Humphreys EB, Mangold LA, et al.
JAMA. 2005;294:433-439.

This study was a retrospective cohort study of 379 men who developed PSA progression after radical prostatectomy at an urban tertiary care referral center between 1982 and 2000. The researchers sought to determine clinical parameters predictive of high risk of death from prostate cancer. Each of the men in this study had available follow-up data (recommended regimen: PSA and digital rectal examination every 3 months for the first year, every 6 months for the second year, and yearly thereafter) and had at least 2 PSA values separated by at least 3 months in the interval after documented PSA progression (PSA $>$ 0.2 ng/mL). Excluded were patients who received preoperative hormonal therapy or radiation therapy (RT), patients who received postoperative hormonal therapy or RT before PSA progression, and patients who achieved a durable PSA response to RT after an initial PSA progression (these men were considered to have local-only recurrence and to have been cured by adjuvant RT). The primary outcome measure was prostate cancer–specific death.

Mean (SD) follow-up was 10.3 (4.7) years, and the median follow-up was 10 years. Eighty-nine percent of patients had extracapsular extension, and only 14% had Gleason score less than 7. The researchers used univariate analysis to determine optimal groupings for Gleason score ($\leq$ 7 vs $\geq$ 8) and time to PSA progression ($\leq$ 3 years vs $>$ 3 years). These along with pathologic variables, PSADT, and patient age were included in a multivariable Cox proportional hazards model and a Kaplan-Meier analysis. The analysis demonstrated a significant association between prostate cancer–specific death and Gleason score ($\geq$ 8 vs $\leq$ 7), time

from surgery to PSA progression (≤ 3 years vs > 3 years), and PSADT (both as a continuous and a categoric variable, grouped by months as < 3.0 vs 3.0–8.9 vs 9.0–14.9 vs ≥ 15.0 months). The difference in the PSADT groups compared with the ≥ 15.0-month group was statistically significant ($P < .05$), except in the 9.0–14.9-month group, in which a trend still remained. Interestingly, the lowest-risk patients (recurrence after 3 years, Gleason score < 8, and PSADT ≥ 15.0 months) can have a 94% (95% CI, 87%-100%) 15-year disease-free survival estimate.

These data might be useful in risk-stratifying patients early, allowing high-risk patients to receive potentially life-prolonging adjuvant therapies and sparing low-risk patients from the morbidity of unnecessary treatment.

The researchers comment that prostate cancer has a long natural history, even after PSA progression. Their data, although based on a small number of patients, might be useful in risk-stratifying patients early, allowing high-risk patients to receive potentially life-prolonging adjuvant therapies and sparing low-risk patients from the morbidity of unnecessary treatment.

Pretreatment PSA Velocity and Risk of Death from Prostate Cancer Following External Beam Radiation Therapy

D'Amico AV, Renshaw AA, Sussman B, Chen MH.
JAMA. 2005;294:440-447.

In the same issue of the *Journal of the American Medical Association*, D'Amico and colleagues reported a study of the predictive properties of pretreatment PSA kinetics, in which they examined the relationship of PSA velocity before RT to prostate cancer–specific mortality. Previously, elevated pretreatment PSA velocity (> 2.0 ng/mL/y) had only been observed to correlate with poor prognosis in surgical series, and PSA velocity had not been assessed in patients who were otherwise low risk. A total of 358 men were identified with T1 and T2 prostate cancer and treated with external beam RT. Excluded were men who had fewer than 2 prior PSA measurements, whose pretreatment PSA measurements were less than 6 months apart, and who received neoadjuvant, concurrent, or adjuvant hormonal therapy. Men were stratified into a low-risk (PSA < 10.0 ng/mL, Gleason score ≤ 6, and clinical stage T1c or T2a) or a high-risk group. The primary endpoint was prostate cancer–specific mortality; secondary endpoints were PSA progression and all-cause mortality. PSA progression was defined by the American Society for Therapeutic Radiology and Oncology criteria. Before PSA progression, PSA measurements were obtained at a median of every 6 months, and digital rectal examination was performed yearly; after PSA progression PSA levels were measured a median of every 4 months. Salvage hormone therapy was initiated at a median PSA level of 9.6 ng/mL (interquartile range, 8.8–9.8 ng/mL).

Median follow-up was 4.0 years (range, 0.2–13.5 years), starting from the last day of RT. Median age was 71.2 years (range, 43.2–83.5 years). One hundred twenty-five men were characterized as low risk, and 233 were high risk. Elevated PSA levels led to diagnosis in 44% of patients. Sixty-eight percent of the group had a PSA level of 10.0 ng/mL or less, whereas the median PSA level was 8.0 ng/mL (range, 0.5–124.5 ng/mL). Overall, 160 men had PSA progression, 79 died, and 30 died from prostate cancer. Cox regression and Kaplan-Meier analyses were used to determine the association of pretreatment variables with study endpoints. The first analysis examined the entire group of patients, testing PSA velocity (first as a continuous variable and then as > 2.0 ng/mL/y vs ≤ 2.0 ng/mL/y), PSA level, biopsy Gleason score (8–10 vs 7 vs ≤ 6), and clinical tumor stage at diagnosis. This analysis demonstrated that PSA velocity greater than 2.0 ng/mL/y when compared with PSA velocity less than or equal to 2.0 ng/mL/y and adjusted for PSA level, biopsy Gleason score, and clinical tumor stage, was significantly associated with shorter time to prostate cancer–specific and all-cause mortality. Of all 30 prostate cancer deaths, 28 occurred in patients with PSA velocity greater than 2.0 ng/mL/y. Controlling for age, the continuous variable PSA velocity maintained a significant association with shorter time to prostate cancer–specific and all-cause mortality. The second analysis examined the association between the same endpoints and pretreatment risk group and PSA velocity. Here PSA velocity was again significantly associated with PSA recurrence, prostate cancer–specific mortality, and all-cause mortality. The 7-year estimate of prostate cancer mortality in the low-risk group was 19% when PSA velocity was greater than 2 ng/mL/y and 0 when PSA velocity was less than 2 ng/mL/y, whereas for the high-risk group prostate cancer mortality was 24% with PSA velocity greater than 2 ng/mL/y and 4% for velocity less than 2 ng/mL/y.

This information allows physicians to stratify risk in patients at the time of diagnosis and to recommend additional therapy for those patients in a high-risk group or having an elevated PSA velocity. Although patients might

have undergone appropriate therapy for localized disease in the form of RT or radical prostatectomy, they might still have a significant risk of an adverse outcome. The investigators suggest that patients with elevated PSA velocity, even with other low-risk characteristics, might benefit from concurrent androgen deprivation therapy when undergoing RT.

As increasing numbers of researchers highlight the limited diagnostic utility of a single PSA value, many are left with the notion that PSA is "not a good test." Studies such as these demonstrate that there is great value in the information provided by PSA, especially if PSA is viewed not simply as a static number but as a dynamic biologic descriptor. ■

Infertility

Freeze that Sperm

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One of the side effects of cancer therapy—be it radiotherapy, chemotherapy, and/or surgery—is a potential detrimental hit to the reproductive system. This could be devastating psychologically to couples in which the male partner has been treated for an oncological disease. The gonads themselves are very susceptible to radiotherapy and chemotherapy, and some surgical procedures destroy or disable the function of the male ductal system, which might result in a lack of seminal emission and/or a ductal obstruction. It is well recognized that the cancer itself might have an impact on the reproductive system, and infertility sometimes might be the presenting complaint of someone with an oncological disease, depending on the tissue affected and the severity of the disease. Thus, when the aforementioned oncological treatments are given to these patients, their fertility status is further compromised. These gonadotoxic effects can be either temporary or permanent. If the former, it can sometimes take 1 to 2 years after the completion of treatment for spermatogenesis to recover. In a number of patients, again depending on the type and duration of therapy, azoospermia might be permanent. As such, it seems prudent that any man who is a potential future father be evaluated with a semen analysis if (1) he is diagnosed with a cancer, and (2) he is to undergo some form of therapy for this tumor.

In Vitro Fertilization–Intracytoplasmic Sperm Injection Success Rates with Cryopreserved Sperm from Patients with Malignant Disease

Revel A, Haimov-Kochman R, Porat A, et al.
Fert Steril. 2005;84:118-122.

In this study, the semen of 21 men was cryopreserved before their cancer treatment, in the hope that the frozen sperm could be used in some fashion in the future. The mean age of these male patients was 33 ± 7 years, the same as their female partners. Of the 21 men, 9 had lymphomas, 4 had sarcomas, 5 had testicular cancers (all underwent orchiectomy), and the remaining 3 had leukemia, prostate cancer, and histiocytoma in the inguinal canal, respectively. Although pretherapy sperm counts were not stated, the postthaw sperm count ranged from 1×10^5 to 106×10^6 motile sperm per milliliter. The longest freezing period was 18 years.

The female partners of all 21 men underwent in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI). Out of 62 IVF procedures there were 26 pregnancies (42%), and from these 26 pregnancies there were 8 spontaneous abortions (31%) and 23 children (13 singletons and 5 pairs of twins). In 12 of the 21 couples (57%), at least 1 pregnancy was achieved. The lowest total motile sperm count that was successful was 1×10^5/mL. The sperm frozen for 18 years was successful in achieving a pregnancy and live birth.

Physicians who deal with men with cancer during their reproductive years need to realize that fertility is a major concern to these men, if not at the time of diagnosis, certainly at some time in the future.

This study highlights the fact that physicians who deal with men with cancer during their reproductive years need to realize that fertility is a major concern to these men, if not at the time of diagnosis, certainly at some time in the future. Therefore, the cryopreservation of sperm at the time of diagnosis, and before any therapy directed against the cancer, should be recommended. Even severely oligospermic men should be offered this opportunity because IVF with ICSI requires 1 sperm per egg. For men with abnormal preoperative sperm counts who are